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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/547,669 | 09/02/2005 | Daniele Calistri | 2503-1170 | 1643 |

466 7590 06/30/2011

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| EXAMINER | |
|---|---|
| STAPLES, MARK | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/30/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 10/547,669 | CALISTRI ET AL. |
| | Examiner | Art Unit |
| | MARK STAPLES | 1637 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04/01/2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,9,10 and 12* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9, and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

| Attachment(s) | |
|---|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ . |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____. | 6) ☐ Other: _____. |

## DETAILED ACTION

1. In view of the Appeal Brief filed on 04/01/2011, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Gary Benzion/
Supervisory Patent Examiner, Art Unit 1637

2. This action is non final.

3. Claims 1, 9, and 10 consonant with original election of SEQ ID NOs: 9, 10, 13, 14, 15, and 16 were examined. Claim 12 remains withdrawn. It is noted that claim 12 is a product claim which has a broader scope than claims 1, 9, and 10 by reciting

"oligonucleotides" beyond the recited primer sequences of claim 1. It is also noted that the user instructions of claim 12 carry no patentable weight.

Applicant has previously amended the claims to recite the use of sequences of SEQ ID NOs: 1-16. As sequences of SEQ ID NOs; 11, 12, and 9-16 were not previously examined, prosecution is reopened in order to examine these sequences. Accordingly, new grounds of rejection are given below.

Claims 1, 9, and 10 are pending and at issue.

## ***Rejection Withdrawn***

### ***Claim Rejections Withdrawn- 35 USC § 103(a)***

4. The rejection of claims 1, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001), Kmiec et al. (W0 2001/73002), Albertsen et al. (US Patent No.: 6,114,124 issued 2001), and Buck et al. (1999) is withdrawn in order to examine the primers of SEQ ID NOs; 11, 12, and 9-16. Applicant's arguments are addressed below in view of the new grounds of rejection.

5. The following table is given for the discussion of prior art which follows.

***Table 2***

(expanded from former Table 1)

P53 gene, 95%-100% Sequence Matches and Exact Lengths for SEQ ID NOs: 1-8

APC gene, 100% Sequence Matches for SEQ ID NOs: 9-16

**P53 GENE PRIMERS**

100% Sequence Matches and Exact Lengths for SEQ ID NOs: 1-4 and 6-8

> 95% Match and Exact Length for SEQ ID NO: 5, one nucleotide mismatch

**Wakamatsu et al. (1999):**

Am. J. Respir. Cell Mol. Biol., Volume 21, Number 2, August 1999 209-215
Frequent Expression of p53 Protein without Mutation in the Atypical Epithelium of Human Bronchus

Kentaro Wakamatsu, Yoichi Nakanishi, Koichi Takayama, Hiroyuki Miyazaki, Kenshi Hayashi, and Nobuyuki Hara

Research Institute for Diseases of the Chest; and Division of Genome Analysis, Institute of Genetic Information, Faculty of Medicine, Kyushu University, Fukuoka, Japan

**Matches:**

```
   CTCTTCCTGCAGTACTCCCCTGC(SEQ ID NO:1)
   |||||||||||||||||||||||
5'-CTCTTCCTGCAGTACTCCCCTGC-3' (sense) exon 5


   GCCCCAGCTGCTCACCATCGCTA (SEQ ID NO:2)
   |||||||||||||||||||||||
5'-GCCCCAGCTGCTCACCATCGCTA-3' (antisense) exon 5

   GATTGCTCTTAGGTCTGGCCCCTC (SEQ ID NO: 3)
   |||||||||||||||||||||||
5'-GATTGCTCTTAGGTCTGGCCCCTC-3' (sense) exon 6

   GGCCACTGACAACCACCCTTAACC(SEQ ID NO: 4)
   |||||||||||||||||||||||
5'-GGCCACTGACAACCACCCTTAACC-3'(antisense) exon 6

   GCGTTGTCTCCTAGGTTGGCTCTG (SEQ ID NO: 5)
   | |||||||||||||||||||||
5'-GTGTTGTCTCCTAGGTTGGCTCTG-3' (sense)exon 7

   CAAGTGGCTCCTGACCTGGAGTC (SEQ ID NO: 6)
   |||||||||||||||||||||||
5'-CAAGTGGCTCCTGACCTGGAGTC-3' (antisense)exon 7

   ACCTGATTTCCTTACTGCCTCTGGC(SEQ ID NO: 7)
   |||||||||||||||||||||||
5'-ACCTGATTTCCTTACTGCCTCTGGC-3' (sense) exon 8

   GTCCTGCTTGCTTACCTCGCTTAGT (SEQ ID NO: 8)
   |||||||||||||||||||||||
5'-GTCCTGCTTGCTTACCTCGCTTAGT-3'(antisense)exon 8
```

**APC GENE PRIMERS**

***SEQ ID NO: 9***

*Shuber*

Search Result 20070214_162645_us-10-547-669a-9.rng.

```
Title:          US-10-547-669A-9
Perfect score:  20
Sequence:       1 aactaccatccagcaacaga 20
RESULT 3

AAF62231/c

ID   AAF62231 standard; DNA; 37 BP.

AC   AAF62231;

DT   21-MAY-2001  (first entry)

DE   Probe for human apc2 (adenomatous polyposis coli) gene.
KW   Human; detection; cancer; pre-cancer; foetal abnormality; apoptosis;
KW   colon cancer; probe; adenomatous polyposis coli; apc; ss.
OS   Homo sapiens.
PN   WO200118252-A2.
PD   15-MAR-2001.
PF   08-SEP-2000; 2000WO-US024639.
PR   08-SEP-1999;   99US-0152847P.
PR   07-DEC-1999;   99US-00455950.
PA   (EXAC-) EXACT LAB INC.
PI   Shuber AP;
DR   WPI; 2001-235215/24.
PT   Detecting a disease (e.g. cancer or pre-cancer), determining its status,
PT   or screening a patient for a disease, comprises determining the
integrity
PT   of nucleic acids in a patient sample containing shed cells or cellular
PT   debris.
PS   Example 3; Page 20; 44pp; English.
CC   A method for determining the disease status of a patient or screening a
CC   patient for disease, comprises determining the integrity of nucleic
acids
CC   in a sample containing cells which have been shed or cellular debris.
The
CC   method is useful for detecting a disease, determining the disease status
CC   of a patient or screening a patient for a disease. The disease may be
CC   cancer (e.g. colon cancer, lung cancer, oesophageal cancer, prostate
CC   cancer, stomach cancer, pancreatic cancer, liver cancer or lymphoma) or
CC   pre-cancer. The methods are also useful for assessing the integrity of
CC   DNA in a biological sample or for assessing foetal abnormalities. The
CC   methods are also useful as assays for apoptosis. The present sequence
CC   represents a probe for human apc2 (adenomatous polyposis coli) DNA,
which
```

```
CC   is used in an example illustrating the use of the method for the
CC   detection of colon cancer
SQ   Sequence 37 BP; 5 A; 5 C; 12 G; 15 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 20;  DB 4;  Length 37;

  Best Local Similarity   100.0%;  Pred. No. 9.3;

Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;


Qy          1 AACTACCATCCAGCAACAGA 20
              ||||||||||||||||||||
Db         35 AACTACCATCCAGCAACAGA 16
```

## ***SEQ ID NO: 9***

*Tamura et al*

Gen Tamura, Chihaya Maesawa, Yasushi Suzuki, et al.
Mutations of the *APC* Gene Occur during Early Stages of Gastric Adenoma Development
*Cancer Res* 1994;54:1149-1151. Published online March 1, 1994.

```
        1 AACTACCATCCAGCAACAGA 20  SEQ ID NO: 9
          ||||||||||||||||||||
          AACTACCATCCAGCAACAGA Upstream primer for segment 3 (Table 1)
```

## ***SEQ ID NO: 10***

Search Result 20070214_162645_us-10-547-669a-10.rng.

```
Title:          US-10-547-669A-10

Perfect score:  20

Sequence:       1 taatttggcataaggcatag 20

RESULT 2

ABA78740

ID   ABA78740 standard; DNA; 121 BP.

AC   ABA78740;
```

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1586.
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.
OS Homo sapiens.
PN WO200173002-A2.
PD 04-OCT-2001.
PF 27-MAR-2001; 2001WO-US009761.
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
PA (UYDE ) UNIV DELAWARE.
PI Kmiec EB, Gamper HB, Rice MC;
DR WPI; 2001-639230/73.
XX
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
PS Claim 7; Page 139; 294pp; English.
CC The present invention provides single-stranded oligonucleotides which
can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention
SQ Sequence 121 BP; 30 A; 20 C; 25 G; 46 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;

Best Local Similarity 100.0%; Pred. No. 3.1;

Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 TAATTTGGCATAAGGCATAG 20
              ||||||||||||||||||||
Db          4 TAATTTGGCATAAGGCATAG 23
```

## ***SEQ ID NO: 11***

```
LOCUS       AC008575         168285 bp    DNA     linear   PRI 20-JUL-2001
DEFINITION  Homo sapiens chromosome 5 clone CTC-554D6, complete sequence.
ACCESSION   AC008575
VERSION     AC008575.7  GI:14971161
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)

Homo sapiens chromosome 5 clone CTC-554D6, complete sequence
Length=168285

 Score = 40.1 bits (20),  Expect = 0.060
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Plus

Query  1       CAGTTGAACTCTGGAAGGCA  20
               ||||||||||||||||||||
Sbjct  128077  CAGTTGAACTCTGGAAGGCA  128096
```

## ***SEQ ID NO: 12***

```
LOCUS       AC008575           168285 bp    DNA     linear   PRI 20-JUL-2001
DEFINITION  Homo sapiens chromosome 5 clone CTC-554D6, complete sequence.
ACCESSION   AC008575
VERSION     AC008575.7  GI:14971161
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)


Homo sapiens chromosome 5 clone CTC-554D6, complete sequence
Length=168285

 Score = 40.1 bits (20),  Expect = 0.060
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1       TGACACAAAGACTGGCTTAC  20
```

```
                ||||||||||||||||||||
Sbjct  128366  TGACACAAAGACTGGCTTAC  128347
```

## ***SEQ ID NO: 13***

Search Result 20070214_162645_us-10-547-669a-13.rng.

```
Title:          US-10-547-669A-13

Perfect score:  20

Sequence:       1 gatgtaatcagacgacacag 20

RESULT 2

ABA78836/c

ID   ABA78836 standard; DNA; 121 BP.

AC   ABA78836;

DT   24-JAN-2002  (first entry)

DE   APC mutation correcting oligonucleotide SEQ ID NO: 1682.
KW   Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW   retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW   cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW   adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW   haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW   mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW   familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW   UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW   Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW   antilipemic; ss.
OS   Homo sapiens.
PN   WO200173002-A2.
PD   04-OCT-2001.
PF   27-MAR-2001; 2001WO-US009761.
PR   27-MAR-2000; 2000US-0192176P.
PR   27-MAR-2000; 2000US-0192179P.
PR   01-JUN-2000; 2000US-0208538P.
PR   30-OCT-2000; 2000US-0244989P.
PA   (UYDE ) UNIV DELAWARE.
PI   Kmiec EB,  Gamper HB,  Rice MC;
DR   WPI; 2001-639230/73.
PT   Oligonucleotide for targeted alterations of genetic sequences and for
PT   treating cystic fibrosis, comprises at least one mismatch and chemical
```

```
PT   modification.
PS   Claim 7; Page 144; 294pp; English.
CC   The present invention provides single-stranded oligonucleotides which
can
CC   be used for the targeted alteration of genomic sequences, where the
CC   oligonucleotide has at least one mismatch compared with the genomic
CC   sequence to be altered. In particular, these sequences are directed at
CC   the following genes: adenosine deaminase, p53, beta-globin,
CC   retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC   (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC   1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC   apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
glucuronosyltransferase
CC   (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC   presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC   such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC   haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC   Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC   various syndromes. The present sequence is one of the gene correcting
CC   oligonucleotides of the invention
SQ   Sequence 121 BP; 30 A; 24 C; 19 G; 48 T; 0 U; 0 Other;


  Query Match             100.0%;  Score 20;  DB 4;  Length 121;

  Best Local Similarity   100.0%;  Pred. No. 1.5;

Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATGTAATCAGACGACACAG 20
              ||||||||||||||||||||
Db         78 GATGTAATCAGACGACACAG 59
```

## ***SEQ ID NO: 14***

```
Search Result 20070214_162645_us-10-547-669a-14.rng

Title:          US-10-547-669A-14
Perfect score:  20
Sequence:       1 ggcaatcgaacgactctcaa 20


RESULT 2

ABA78883/c

ID   ABA78883 standard; DNA; 121 BP.

AC   ABA78883;

DT   24-JAN-2002  (first entry)
```

DE APC mutation correcting oligonucleotide SEQ ID NO: 1729.
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.
OS Homo sapiens.
PN WO200173002-A2.
PD 04-OCT-2001.
PF 27-MAR-2001; 2001WO-US009761.
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
PA (UYDE ) UNIV DELAWARE.
PI Kmiec EB, Gamper HB, Rice MC;
DR WPI; 2001-639230/73.
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
PS Claim 7; Page 146; 294pp; English.
CC The present invention provides single-stranded oligonucleotides which
can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locu
s
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention
SQ Sequence 121 BP; 28 A; 29 C; 28 G; 36 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;

Best Local Similarity 100.0%; Pred. No. 2.1;

Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 GGCAATCGAACGACTCTCAA 20
              ||||||||||||||||||||
Db         92 GGCAATCGAACGACTCTCAA 73
```

## ***SEQ ID NO: 15***

```
Search Result 20070214_162645_us-10-547-669a-15.rng.

Title:          US-10-547-669A-15
Perfect score:  20
Sequence:       1 cagtgatcttccagatagcc 20


RESULT 5

AAA93450

ID   AAA93450 standard; cDNA; 8229 BP.

AC   AAA93450;

DT   16-JAN-2001  (first entry)
```

DE Human APC (DP2.5) cDNA (splice variant 2).

```
KW   APC gene; Adenomatous Polyposis Coli gene; human; chromosome 5q21;
KW   familial adenomatous polyposis; FAP locus; Gardner's syndrome; GS;
KW   sporadic tumour; adenoma; carcinoma; cancer; lung; breast; colon;
rectum;
KW   bladder; liver; sarcoma; stomach; prostate; leukaemia; lymphoma;
KW   tumour suppressor; anti-APC antibody; detection; diagnosis; prognosis;
KW   genetic predisposition; drug screening; DP2.5; splice variant; ds.
OS   Homo sapiens.
PN   US6114124-A.
PD   05-SEP-2000.
PF   25-MAY-1995;   95US-00450582.
PR   16-JAN-1991;   91GB-00000962.
PR   16-JAN-1991;   91GB-00000963.
PR   16-JAN-1991;   91GB-00000974.
PR   16-JAN-1991;   91GB-00000975.
PR   08-AUG-1991;   91US-00741940.
PR   12-AUG-1994;   94US-00289548.
PA   (ICIL ) IMPERIAL CHEM IND PLC.
PA   (UYJO ) UNIV JOHNS HOPKINS.
PA   (UTAH ) UNIV UTAH.
PA   (CANC-) CANCER INST.
PI   Carlson M,  Groden J,  Joslyn G,  Kinzler K,  Markham AF,  Anand R;
PI   Albertsen H,  White RL,  Thliveris A,  Nakamura Y,  Vogelstein B;
PI   Hedge PJ;
DR   WPI; 2000-565003/52.
DR   P-PSDB; AAB23012.
PT   Detecting Adenomatous Polypopsis Coli (APC) protein in a sample for
```

PT diagnosing cancers, involves contacting the sample with antibodies that
PT specifically bind to APC protein and detecting the complex formed.
PS Example 7; Fig 7A1-7W; 125pp; English.

CC The invention relates to a novel method for detecting Adenomatous
CC Polyposis Coli (APC) protein in a sample. The method involves contacting
CC the sample with antibodies which specifically binds to the 2843 amino
CC acid form of the human APC protein, or to a mutant APC protein, and
CC detecting an APC-antibody complex. Mutations in the APC gene play a role
CC in tumorigenesis, indicating that it is a tumour suppressor gene. It is
CC located on chromosome 5q21, which corresponds to the FAP (familial
CC adenomatous polyposis) locus. FAP is an autosomal dominant inherited
CC disease in which affected individuals develop hundreds to thousands of
CC adenomatous polyps in the colon and rectum, some of which progress to
CC malignancy. The FAP locus is often found to be deleted in sporadic
(i.e.,
CC non-familial) adenomas and carcinomas, and chromosome 5q deletions have
CC also been observed in tumours of the lung, breast, colon, rectum,
CC bladder, liver, sarcomas, stomach, and prostate, and in leukaemias and
CC lymphomas. Although the FAP locus contains several other genes such as
CC FER, TB1, TB2, and MCC, it is thought that mutations in the APC gene
play
CC a key role in the development of FAP and sporadic tumours. The method is
CC useful for detecting APC protein and its mutant forms in foetal tissue,
CC placental tissue, amniotic fluid, blood, serum or a tumour sample. The
CC method is useful for diagnosing or prognosing neoplastic tissue, for
CC detecting a genetic predisposition to cancer, for detecting germline and
CC somatic alteration of wild-type APC genes, and for testing therapeutic
CC agents for the ability to suppress tumours. The present sequence
CC represents cDNA encoding a 2742 amino acid splice variant of the human
CC APC protein

SQ Sequence 8229 BP; 2863 A; 1702 C; 1670 G; 1994 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 3; Length 8229;

Best Local Similarity 100.0%; Pred. No. 9.8;

Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 CAGTGATCTTCCAGATAGCC 20
              ||||||||||||||||||||
Db       3957 CAGTGATCTTCCAGATAGCC 3976
```

## ***SEQ ID NO: 16***

Search Result 20070214_162645_us-10-547-669a-16.rng.

Title: US-10-547-669A-16

Perfect score: 20

Sequence: 1 aaatggctcatcgaggctca 20

RESULT 2

ABA78900

ID ABA78900 standard; DNA; 121 BP.

AC ABA78900;

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1746.
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.
OS Homo sapiens.
PN WO200173002-A2.
PD 04-OCT-2001.
PF 27-MAR-2001; 2001WO-US009761.
PR 27-MAR-2000; 2000US-0192176P.
PR 27-MAR-2000; 2000US-0192179P.
PR 01-JUN-2000; 2000US-0208538P.
PR 30-OCT-2000; 2000US-0244989P.
PA (UYDE ) UNIV DELAWARE.
PI Kmiec EB, Gamper HB, Rice MC;
DR WPI; 2001-639230/73.
PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.
PS Claim 7; Page 147; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,

```
CC   apolipoprotein E (APOE), LDL receptor (LDLR), UDP-
glucuronosyltransferase
CC   (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC   presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC   such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC   haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC   Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC   various syndromes. The present sequence is one of the gene correcting
CC   oligonucleotides of the invention

SQ   Sequence 121 BP; 38 A; 26 C; 24 G; 33 T; 0 U; 0 Other;


  Query Match             100.0%;  Score 20;  DB 4;  Length 121;

  Best Local Similarity   100.0%;  Pred. No. 1.9;

Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;


Qy          1 AAATGGCTCATCGAGGCTCA 20
              ||||||||||||||||||||
Db         24 AAATGGCTCATCGAGGCTCA 43
```

## ***New Rejections***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (WO 2001/42502 published 2001), Tamura et al. (1994 newly cited), Kmiec et al. (W0 2001/73002 published 2001), GENBANK (2001 Acession no. AC008575, newly cited), Albertsen et al. (US Patent No.: 6,114,124 issued 2001), Wakamatsu et al. (1990, newly cited) as further evidenced by Kim et al. (2001, newly cited), Buck et al. (1999), and Wang et al. (published March 5, 2002 and newly cited).

Regarding claims 1 and 9, Shuber teaches a method for determining the presence of colorectal tumors in a human subject (entire reference), which comprises:
a) extracting DNA from stool samples (see p. 18, 1st paragraph: "After homogenization, nucleic acid is preferably isolated from the stool sample. . . .The extracted nucleic acids are then precipitated with alcohol. . . . Total DNA is isolated using techniques known in the art");
b) PCR amplifying at least three different DNA fragments with a length of 100 base pairs or more, using deoxynucleotide triphosphates or primers labeled with detectable markers (see p. 4, 2nd paragraph, 6th sentence: "It is preferable that, in the case of DNA, the amplification reaction is a polymerase chain reaction (PCR) . . ." ; p. 9, 2nd paragraph : "Methods of the invention also comprise conducting a series of amplification reactions at a series of different genomic loci. . . . Preferably, from about 2 to about 7 amplification reactions on about 2 to about 7 loci are used. . . . In a preferred

embodiment, the target fragment lengths are 200 bp, 400 bp, 800 bp, 1.3 Kb, 1.8 Kb, and 2.4 Kb" which are more than 100 base pairs and note that 200 and 400 are between 100 and 500 base pairs as recited in instant claim 5; and p. 8, 2nd paragraph, 3rd sentence: "Labels, such as fluorescent or radioactive labels, may be used" which also applies to instant claim 2):

i) where p53 gene fragments/loci including exons 5, 7, and 8 are amplified (see p. 8 lines 15-16 and p. 20 lines 1-17), and

ii) where APC gene fragments/loci are amplified (see p. 8 lines 15-16 and p. 20 lines 1-17);

c) quantifying the amplified fragments (amplicons);

d) calculating the total amount of different amplicons;

e) comparing the values obtained in (d) with a reference value (for steps c, d, and e see Figures 1 through 10, where quantitation is given as "Q#", which is calculated by interpolation, as recited in instant claim 9, from a standard curve consisting of known amounts of DNA, and compared to the "NEG CONTROL" as a reference value, and in Figures 1-7 is also compared to the "POSITIVE CONTROL" as another reference value). Shuber further teaches that a total amount of amplicons, that is amplifiable nucleic acid, is indicative of disease by teaching: "As shown in those figures [11A and 11B], patients with [colorectal] cancer or adenoma have an increased yield of amplifiable DNA." (see p. 22 lines 20 and 21).

Further regarding claim 1, Shuber teaches as noted above, including amplification of APC fragments and teaches a sequence comprising SEQ ID NO: 9 (see

Table 2). Shuber et al. teaches the recited fluorescent markers by teaching: "Labels, such as fluorescent or radioactive labels, may be used" (see 3rd sentence of the 2nd paragraph on p. 8, line 19).

Further regarding claim 1, Shuber teaches a method where the reference value is determined from healthy (normal) subjects/patients (See p. 3, 2nd paragraph, 5th sentence: "Thus, tumor cells are typically intact and routinely are shed into, for example, stool, sputum, urine, bile, pancreatic juice, and blood. Such shed cells and cellular debris contain higher integrity nucleic acids and other cellular components compared to those found in specimens obtained from a healthy patient"; and see p. 10, 2nd paragraph, 3rd sentence: "A baseline for comparison of the extent of nucleic acid amplification can be amounts of nucleic acids from known normal samples").

Further regarding claim 1, Shuber teaches a method wherein at least 8 different DNA fragments are amplified (12 loci for amplification are taught which is at least eight, as given on p. 8, 1st paragraph, last sentence: "Preferred disease-associated loci include p53, apc, MSH-2, dcc, scr, c-myc, B-catnenin, mlh-1 , pms-l , pms-2, pol-delta, and bax").

Furthermore the optimization of amplification through selection of primer sequences, placement of primer seuqences, and other factors affecting results for cancer detection was known in the prior art as taught by Shuber:

> "Each of the methods described above are based upon the principle that an intact nucleic acid, or a segment of an intact nucleic acid, in a sample is diagnostic. Thus, variations on the methods described above are contemplated. Such variations include the **placement of primers**, the number of primers used, the target sequence, the **method for identifying sequences, and others**. For example, in the method depicted in Figure 13, and described above, it is not

necessary that the numbers of forward and reverse primers be equal. A forward primer may, for example, be used to amplify fragments between two reverse primers. **Other variations in primer pair placement** are within the skill in the art, as are details of the amplification reactions to be conducted. Finally, as represented in Figures 12 and 13, capture probes may be used in methods of the invention in order to isolate a chosen target sequence" (emphasis by Examiner, see the 1st paragraph on p. 17).

Shuber does not teach other elected APC sequences of instant claim 1 comprising SEQ ID NOs: 10-16. Shuber does not specially teach claimed p53 gene primers of instant SEQ ID NOs: 1-8.

Regarding claim 10, Shuber teaches spectrophotometric detection systems (see p. 8, 2nd paragraph, 3rd sentence: "The amounts of amplification product produced may be compared to standard amounts by any suitable or convenient means, including, but not limited to... machine-driven optical comparison, densitometry,.., and other known means").

***Primer for APC Gene Fragment, SEQ ID NO: 9***

Regarding claim 1, Tamura et al. teach a primer with a sequence identical to SEQ ID NO: 9 for amplifying an APC gene fragment (see upstream primer for segment 3 in Table 1) for determining colorectal tumorigenesis in human patients (see Abstract).

```
1 AACTACCATCCAGCAACAGA 20  SEQ ID NO: 9
  ||||||||||||||||||||
  AACTACCATCCAGCAACAGA Upstream primer for segment 3 (Table 1)
```

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Shuber by for amplifying APC gene fragments/loci with primers by using the upstream primer for amplifying an APC fragment as suggested by Tamura et al. with a reasonable expectation of success. The motivation to do so is provided by Tamura et al. who teach. That the upstream primer can amplify mutations of the APC gene for early detection of colorectal tumor genesis (see last paragraph on p. 1150) Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

**Primers for APC Gene Fragments, SEQ ID NOs: 10-16**

Shuber teaches as noted above, including amplification of APC fragments and teaches a sequence comprising SEQ ID NO: 9 (see Table 2).

Shuber does not teach other elected sequences of instant claim 1 comprising SEQ ID NOs: 10-15 and 16.

Kmiec et al. teach sequences comprising SEQ ID NO: 10 and 16, and teaches sequences comprising the sequences in primer pairs SEQ ID NOs: 13 and 14 (see Table 2 above).

Kmiec et al. do not teach SEQ ID NOs: 9 and 15 or sequences comprising these.

GENBANK teaches sequence AC008575 comprising SEQ ID NOs: 11 and 12 (see Table 2).

Albertsen et al. teach a sequence comprising SEQ ID NO: 15 (see Table 2).

Buck et al. do not teach SEQ ID NOs: 9, 10, 13, 14, 15, or 16; or sequences comprising these.

Claim 1 is rejected for SEQ ID NOs: 10-16, as described following. With regard to Claim 1, for primers designed for amplification of APC gene, Shuber, Kmeic et al., GENBANK, and Albertsen et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 10-16 of the instant invention. It is noted that the instant primer sites of SEQ ID NOs: SEQ ID NO: 10-16 are contained within the sequences disclosed by Shuber, Kmeic et al., GENBANK, and Albertsen et al.

It is noted that Tamura et al. teach a primer of the exact sequence of instant SEQ ID NO: 9 for amplification of a segment of the APC gene. Thus the instant primer of SEQ ID NO: 9 was known in the prior art. However, Shuber also disclose a sequence comprising instant SE ID NO: further making instant SEQ ID NO: obvious for use as primers as given for SEQ ID NOs: 10-16 as follows.

The above described references do not specifically disclose the identical primer sequences of SEQ ID NO: 10-16 of the primers pairs, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art

compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states “The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all

possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Further regarding the APC primer sequences and also p53 primer sequences, Wang et al. teach primer involving obtaining exon sequences from databases, identifying mutation frequencies that above background (see *Statistical Analysis* on p. 3077) to increase sensitivity of mutation detection (see last full sentence on p. 3077), further teach an approach for mutation discovery (see Figure 1), teach detection of colorectal cancer and highlight specific mutations that drive neoplasia including for mutations of APC and p53 genes (see 3rd, 5th, and 6th sentences in the 2nd column on p. 3079).

It would have been further obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods for detecting colorectal cancer with primers to p53 and APC genes of Shuber, Kmeic et al., GENBANK, and Albertsen et al., and Buck et al. by designing the primers to p53 and APC genes for specific and sensitive detection of colorectal cancers as suggested by Wang et al. with a reasonable expectation of success. The motivation to do so is provided by Wang et al. who teach that they developed simple statistical tools to" . . . rigorously determine whether the number of observed mutations in a gene of interest is significantly above the expected background mutation frequency" (see last sentence on p. 3079). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

**Primers for P53 Gene Fragments, SEQ ID NOs: 1-8**

Regarding claim 1, Wakamatsu et al. teach a panel of primers of instant SEQ ID NOs: 1-4 and 6-8 respectively and teach a primer with only one mismatch of instant SEQ ID NO: 5 (see Table 2 above) for amplification p53 Gene fragments which are exons 5, 6, 7, and 9 for point mutations in lung cancer which are concomitant in colorectal tumorigenesis (see 2nd paragraph on p. 209 and see the section *PCR-SSCP* Analysis on p. 211).

Kim et al. provide further evidence that the primers disclosed by Wakamatsu et al. were well known in the prior art by disclosing the very same panel of primers (see section 2.3.2 on p. 215).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods for amplifying p53 gene fragments including exons 5, 7, and 8 and APC gene fragments of Shuber, Tamura et al., Kmiec et al., Albertsen et al., and Buck et al. in combination for detection of colorectal tumors by using the panel of primers for amplification of p53 gene fragments which are exons 5, 6, 7, and 8 as suggested by Wakamatsu et al. with a reasonable expectation of success. The motivation to do so is provided by Wakamatsu et al. who teach that their panel of p53 primers permits the detection of mutations found in cancer. Furthermore as both Shuber and Wakamatsu et al. teach the importance of amplifying fragments of at least exons 5, 7, and 8 of the p53 gene with panels of primers for detection of colorectal tumorigensis; it would have been obvious top one of ordinary skill in the art at the time of the claimed invention to try the primer panel of Wakamatsu et al. in the methods of

Shuber et al. for the detection of colorectal tumorigenesis with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

## ***Response to Arguments***

*Relevant Citations of Precedents*

"Obviousness does not require absolute predictability of success .... [A]ll that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988). The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made. Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000).

"[T]he discovery of an optimum value of a variable in a known process is usually obvious." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1368 (Fed. Cir. 2007). The rationale for determining the optimal parameters for prior art result effective variables "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" Id., quoting In re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

"One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995).

> [E]ven though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the

> capabilities of one skilled in the art, unless the claimed ranges "produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art."

In re Huang, 100 F.3d 135, 139 (Fed. Cir. 1996) (citations omitted). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." In re Baxter Travenol Labs., 952 F.2d 388,392 (Fed. Cir. 1991).

*Shuber*

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "FL-DNA analysis") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant also cites the Neoplasia article filed February 15, 2010 as evidence of the superiority of "FL-DNA" analysis. However as given above "FL-DNA" analysis is not recited in the claim nor are the claims limited to this analysis and thus this particular evidence does not exclude the prior art teachings, especially those of Shuber.

Furthermore the methods of Shuber (i) based on agarose gel electrophoresis with fluorescent labels or (ii) based on other disclosed methods with fluorescent labels (see rejection above) are encompassed by the claims. Additionally, Applicant has failed

to show or provided evidence that the fluorescent methods as recited in claim 1 would yield any superior result over the prior art fluorescent methods disclosed by Shuber.

Applicant has further failed to show in the Affidavits filed 04/01/2011 that the primers as recited in claim 1 would yield any superior result over the prior art primers as disclosed by Shuber or other primers disclosed in the cited prior art. Instead Applicant compares the primers of the instant SEQ ID NOs. to “new” primers which do not appear in the cited prior art. Thus Applicant has not made a comparison to closest prior art (see MPEP 716.02(e) [R-2] Comparison With Closest Prior Art).

Applicant further argues that one would not have looked to Shuber who teaches an “agarose gel electrophoresis” method for a fluorescent method. However, Shuber specifically teaches that fluorescent labels can be used in his methods as given above. Additionally, Shuber is not solely relied upon for teaching fluorescent methods.

Both Shuber and Buck et al. teach that primers can be made to different fragments of known sequences by one of ordinary skill in the art. Applicant has not demonstrated that the selection of the primers sequences as recited in claim 1 are other than those which would have been obvious to one of ordinary skill in the art at the time of the claimed invention with a reasonably expectation of success in amplification of the known sequences.

Applicant further argues, but does not provide evidence, that the fluorescent compound which is ethidium bromide of Shuber would not yield results as good as methods with “FL DNA analysis”. Furthermore, the claims are not limited to "FL DNA analysis" methods as given above.

As Shuber teaches fluorescent methods for determining the presence of colorectal tumors, it is reasonable that one of ordinary skill in the art would have looked to Shuber for guidance on fluorescent methods for determining the presence of colorectal tumors.

*Kmiec and Alberstsen*

Applicant argues that neither Kmiec nor Albersten would have led one skilled in the art to the particular primer or would have indicated that any of the primers should be prepared. However neither Kmiec nor Albersten alone or in combination is solely relied upon for obtaining a particular primer from a known sequence. The other cited prior art is relied upon as well as given above and further below.

*Buck et al.*

Applicant present two main arguments against the teachings of Buck et al. The first argument is that Buck teaches equivalence of primer function for amplification for sequence analysis for qualification and not quantitation. However Buck et al. teach fluorescent labels, specifically rhodamine, (see Table 3) similar to the fluorescent labels used by Shuber. Additionally Buck et al. is not solely relied upon for quantitating the amount of amplicon. Shuber is also relied upon and specifically teaches the use of standard curve to quantify the amount of amplicon (see rejection above). Furthermore, as with Buck et al., Shuber similarly teach primer design by teaching: “Primers are

designed to amplify the locus or loci chosen for analysis" (see p. 4 lines 19-20) , further teaching: "Preferred methods of the invention also comprise conducting amplification reactions on a series of different genomic loci. Preferably, from about 2 to about 7 loci are used. . . . According to methods of the invention, primers are designed to amplify 15 nucleic acid (preferably DNA) at each of the chosen loci." (see p. 9 lines 10-15 and see also p. 5 lines 7-10).

Applicant second main argument is that Buck et al. amplifies "high quality" DNA whereas the claimed invention simplifies "generally poor quality" DNA extract from stool samples. However Buck et al. is not solely relied for teaching the amplification of DNA extracted from stool samples. Shuber is also relied upon who teach extracting DNA from stool for amplification and that: "Total DNA is isolated using techniques known in the art" (see p. 18 lines 3-14). Applicant argues that Buck et al. teaches away from a stool sample but no such teaching is found in Buck et al. Furthermore in view of the newly cited teachings of Wang et al., it would have been obvious to one of ordinary skill in the art at the time of the claimed invention as Wang et al. teach primer design for p53 and APC gene fragments to detect colorectal cancer and teach they have developed simple statistical tools for specific direction to" . . . rigorously determine whether the number of observed mutations in a gene of interest is significantly above the expected background mutation frequency" (see last sentence on p. 3079).

*The Combination and Arguments against Individual Reference*

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues again the primers as recited in the claims give high sensitivity and specificity when compared to a series of new primers. However as given above and given below, Applicant has not compared the results of the primers as recited to the primers of the closest prior art.

Furthermore, "[T]he discovery of an optimum value of a variable in a known process is usually obvious." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1368 (Fed. Cir. 2007). In the instant assuming arguendo that the claimed primer sequences are more optimal for sensitivity and specificity and artisan would have known from the prior art, especially Shuber, Buck et al., and Wang et al that the selection of primer sequences from a known sequence could be improved to increase amplification and to improve detection of colorectal cancer. Buck et al. teaches that primers can be design through the parameter of “secondary priming potential” to yield very high quality results (see 1st full paragraph on p. 534) and that certain other parameters were misleading (see 2nd full paragraph on p. 535). Buck et al. also recommend software programs for primer

design (see 2nd paragraph on p. 535). Wang et al. give specific direction, as noted above, to improve detection of mutation associated with colorectal cancer.

*p53 Primers were known, newly cited Wakamatsu et al.*

*as further evidenced by Kim et al.*

As newly cited, Wakamatsu et al. as further evidenced by Kim et al. disclose the same panel of p53 primer as recited in instant claim 1 with the exception of one nucleotide being different for the primer sequence of instant SEQ ID NO: 5. Based upon these teachings and the current record, it is reasonably expected that the later sequence of Wakamatsu et al. as further evidenced by Kim et al. and not SEQ ID NO: 5, would be the exact complement of the p53 fragment to be amplified, and thus would be superior over the inexact complement of instant SEQ ID NO: 5 in primer amplification of the p53 fragment.

Furthermore the evidence presented in the Affidavits filed 04/01/2011 is insufficient to overcome the cited prior art as there is no comparison of the instant primer sequences to the closest prior art of newly cited Wakamatsu et al. as further evidenced by Kim et al. (see MPEP 716.02(e) [R-2] Comparison With Closest Prior Art). The comparison would have to be at least to the panel of primers for p53 fragments disclosed by Wakamatsu et al. and additional primers for APC fragments as also found in the prior art, including at least the APC primer of Tumura et al. with an exact match to the primer of instant SEQ ID NO: 9.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

## ***Requirement for Information under 37 CFR 1.105***

9. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

Applicant is requested to supply the following information used in the invention process. Applicant is requested to supply a copy of any non-patent literature, published application, or patent (U.S. or foreign) that was used in the invention process, for designing and/or in obtaining the primer sequences of SEQ ID Nos. 1-16. Applicant is also requested to supply the same information regarding the "New" primers as referenced in the Affidavits filed 04/01/2011.

Applicant is requested to supply the following information used in the invention process. Applicant is requested to specifically state which primer sequences, by specific SEQ ID NO as recited in instant claim 1, were used to in the methods described in the Affidavits filed 04/01/2011. Applicant is also requested to supply the raw data and the methods of analysis of the raw data to the extent that one would readily be able to analyze the raw data de novo in order to determine at least the sensitivity and specificity numbers as reported in Table 2 on p. 4 of the Affidavit filed 04/01/2011. This request also encompasses the essential steps as to how the final result is "normalized", as found in the last paragraph on p. 4 of the Affidavit filed 04/01/2011. Presently, it is

unclear from the Affidavit how a result obtained on a 10-20 mg sample can be normalized to the final result of a 4 gr sample by multiplication by a factor of 3. Clarification is requested.

## ***Conclusion***

10. No claim is free of the prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Primary Examiner, Art Unit 1637
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